Pediatric Acute Q Fever in Rural Wisconsin: A Case Report

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ABSTRACT

Introduction: Q fever is a zoonotic disease with a variable clinical presentation and potentially fatal complications. While rare, it is more common in rural areas due to its transmission from animals, including cattle.

Case Presentation: A 3-year-old boy presented in December 2020 with intermittent fevers, headache, rash, and lymphadenopathy. After several months of symptoms, he was diagnosed with acute Q fever.

Discussion: This case demonstrates the importance of considering Q fever in the differential diagnosis when a patient presents with nonspecific infectious symptoms and an epidemiological link that places them at risk.

Conclusions: While rare, Q fever is a potentially serious infection that can affect people living in Wisconsin's rural farming communities.

INTRODUCTION

Q fever is a zoonotic disease caused by the bacterium *Coxiella burnetii.* Humans typically become infected by inhaling air that has been contaminated by waste products of infected animals. It most commonly presents as a febrile influenza-like illness, often with headache; it also may cause pneumonia and hepatitis. Signs and symptoms are often variable and nonspecific, making it difficult to diagnose. Approximately 50% of infections are asymptomatic, leading to significant underreporting.[1] Persistent localized Q fever, previously classified as chronic Q fever, is estimated to occur in less than 5% of persons who are initially infected and may occur after symptomatic or asymptomatic infections. Here, we present a child with a prolonged course of relapsing febrile illness eventually diagnosed as acute Q fever.

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CASE PRESENTATION

In December 2020, a 3-year-old boy with no pertinent past medical history presented to the clinic with a 1-day history of submandibular lymphadenopathy, fatigue, and subjective fever. Exam was notable for bilateral cervical lymphadenopathy but otherwise normal. He tested negative for SARS-CoV-2 and group A streptococcal pharyngitis and was presumed to have a nonspecific viral infection. Two weeks later, he was seen in the emergency department (ED) for persistent symptoms of fever and submandibular lymphadenopathy. Exam revealed a prominent right-sided submandibular lymph node but was otherwise unremarkable. A neck ultrasound revealed multiple enlarged lymph nodes with normal echotexture and no evidence of a fluid collection or abscess. A complete blood cell count (CBC) was normal, except for a mild normocytic anemia. A urinalysis was normal. A heterophile antibody for infectious mononucleosis and *Bartonella henselae* titer were negative. He was diagnosed with lymphadenitis and treated with a 7-day course of amoxicillin-clavulanate.

Over the next 6 weeks, the patient was seen multiple times in the ED and his primary care clinic with recurrent fevers, lymphadenopathy, headache, malaise, and a diffuse erythematous maculopapular rash on extremities and trunk. Further workup included uric acid, lactate dehydrogenase, CBC, complete met

Figure. Centers for Disease Control and Prevention Surveillance Case Definition and Case Classification for Acute and Persistent Localized Q Fever

	Acute Q fever	Chronic Q fever
Clinical evidence of infection	Fever and one or more of the following: rigors, severe retrobulbar headache, acute hepatitis, pneumonia, or elevated liver enzymes	Newly recognized culture-negative endocarditis (particularly in a patient with previous valvulopathy or compromised immune system), suspected infection of a vascular aneurysm or vascular prosthesis, or chronic hepatitis, osteomyelitis, or pneumonitis in the absence of other known etiology
Laboratory criteria[a,b]	**Laboratory confirmed (one or more of the following):** • Fourfold change in IgG antibody titer to *Coxiella burnetii* phase II antigen by IFA between paired sera • Detection of *C burnetii* DNA in a clinical specimen by PCR • Demonstration of *C burnetii* in a clinical specimen by IHC • Isolation of *C burnetii* from a clinical specimen by culture	**Laboratory confirmed (one or more of the following):** • IgG titer ≥1:800[c] to *C burnetii* phase I antigen by IFA • Detection of *C burnetii* DNA in a clinical specimen by PCR • Demonstration of *C burnetii* in a clinical specimen by IHC • Isolation of *C burnetii* from a clinical specimen by culture
	Laboratory supportive (one or more of the following): • Single IgG titer ≥1:128 to *C burnetii* phase II antigen by IFA (phase I titers may be elevated as well) or • Elevated phase II IgG or IgM antibody reactive with *C burnetii* antigen by ELISA, dot-ELISA, or latex agglutination	**Laboratory supportive:** • IFA IgG titer ≥1:128 and <1:800[c] to *C burnetii* phase I antigen
Case classification	**Confirmed acute Q fever:** Laboratory-confirmation with clinical evidence of infection or an epidemiological link to a laboratory-confirmed case	**Confirmed chronic Q fever:** Clinical evidence of infection with laboratory confirmation
	Probable acute Q fever: Clinical evidence of infection with laboratory-supportive results	**Probable chronic Q fever** Clinical evidence of infection with laboratory-supportive results

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IFA, indirect immunofluorescence antibody assay; IgG, immunoglobulin G; IgM, immunoglobulin M; IHC, immunohistochemistry; PCR, polymerase chain reaction.

[a]CDC prefers simultaneous testing of paired samples. IgM tests are not strongly supportive of serodiagnosis because the response might be persistent (making it unreliable as an indicator of recent infection) or nonspecific (resulting in false positives). ELISA tests are not quantitative and cannot be used to measure changes in antibody titer; thus, they can only be used for classification of probable cases. Performing laboratories determine the appropriate cutoff titers for ELISA. Serologic test results should be interpreted with caution because baseline antibodies acquired as a result of previous exposure to Q fever might exist, especially in patients with rural or farming backgrounds.

[b]Patients with suspected chronic Q fever should be evaluated for titers both to phase I and phase II antigens. Serologic test results should be interpreted with caution because baseline antibodies acquired as a result of previous exposure to Q fever might exist, especially in patients with rural or farming backgrounds.

[c]US laboratories use a twofold dilution scheme that does not result in a titer equaling 800; in this document, a titer of 1024 is used as the replacement.

Reprinted from the Centers for Disease Control and Prevention: Diagnosis and Management of Q Fever — United States, 2013 Recommendations from CDC and the Q Fever Working Group, Table 3.[1]

abolic panel, C-reactive protein, and erythrocyte sedimentation rate, along with Epstein–Barr virus and cytomegalovirus serologies. Findings included a white blood cell count of 15.6 K/μL and platelets of 452 K/μL, with all other results normal.

The patient's social history was significant for living on a dairy farm with his parents. His mother reported handling of placenta and birth fluids during calving season prior to the development of her son's signs and symptoms. She said he was present in the maternity pen while cattle were birthing. The family also regularly consumed unpasteurized cow's milk from their farm.

The patient's mother discussed her son's symptoms with their veterinarian, who mentioned that another local dairy farmer recently had been diagnosed with Q fever after presenting with similar nonspecific signs and symptoms. Given this new information, our patient was subsequently tested for Q fever by obtaining phase I and phase II IgG antibody titers. While awaiting those results, he continued to have intermittent fever, rash, and lymphadenopathy. Pediatric infectious disease was consulted. Additional serologies for *Toxoplasma, Brucella,* parvovirus B19, and tularemia were negative. The patient's Q fever IgG titers revealed a phase I titer of 1:256 and a phase II titer of 1:2048, and he was diagnosed with acute Q fever. He was treated with a 14-day course of doxycycline, and his case was reported to both the local and state public health departments. His symptoms quickly resolved. Repeat titers at 1 and 3 months posttreatment remained stable without evidence of an increasing phase I titer. His 12-month titers were decreased at 1:128 for phase I and 1:256 for phase II. He had a normal echocardiogram in March 2022.

In February 2021, the patient's mother presented with headaches, neck pain, abdominal pain, and nausea, and had positive serology testing with phase I titer of 1:128 and phase II titer of 1:512. Given her signs and symptoms, positive serology, and similar exposure history as our patient, it was presumed that she had acute Q fever, and she received treatment with doxycycline. She had rapid resolution of her symptoms, and her titer nor-

malized on recheck 3 months later. Then, 4 months later, the patient's father and another worker on the farm were both diagnosed with and treated for Q fever.

DISCUSSION

Q fever is a reportable disease in the United States, although it is likely underreported due to misdiagnosis or asymptomatic and mild disease not prompting medical evaluation. Over the last 3 years, an average of 2 acute Q fever cases per year and 0 to 2 persistent localized Q fever cases were reported in Wisconsin (Wisconsin Department of Health Services, unpublished data). In 2019, 178 cases were reported to the Centers for Disease Control and Prevention.[2]

Coxiella burnetii, the causative organism of Q fever, is an intracellular gram-negative bacterium that is extremely hearty and virulent; a single organism is considered sufficient to cause disease and, thus, is considered a potential bioterrorism agent.[1] Transmission is typically via inhalation of contaminated aerosols. Animal reservoirs include ruminants, such as cattle, sheep, and goats, which frequently manifest with reproductive difficulties, such as low birth weight and abortions—especially at late gestation.[3] Human infection may be either from direct exposure to animal birth products, urine, or feces; consumption of unpasteurized milk of infected animals; or indirectly from contaminated dust in barns or birthing stalls.[3] Rarely, tickborne transmission has been reported.[4] In this case, our patient regularly consumed unpasteurized milk and was exposed to birthing cattle.

Coxiella burnetii has an incubation period of 2 to 3 weeks in humans, although the incubation period can be variable based on the inoculum dose. Of the 50% who manifest signs and symptoms, acute Q fever is most commonly a self-limited influenza-like illness of high fever, chills, myalgias, and headaches. Fevers can be acute or may last for weeks, as in this case. A generally mild, viral-pattern pneumonia also may develop and rarely can progress to more severe respiratory failure. Hepatitis without jaundice may present with fever and transaminase elevations. Rarely, immune-mediated endocarditis may occur, and persistent infection can result in chronic or subacute endocarditis. The mortality rate of untreated acute Q fever is 1% to 2%, as many cases are self-limited.[1]

Children have lower rates of symptomatic acute Q fever compared to adults, and their symptomatic infections tend to be milder.[1] Children commonly present with a febrile illness and headache, as in our patient. They are more likely than adults to have gastrointestinal and dermatologic presentations. While most acute Q fever cases in children are self-limited, there are cases of recurrent, relapsing febrile illnesses, similar to our case presentation.

Persistent localized Q fever may develop months to years after either symptomatic acute Q fever or asymptomatic infection. It typically manifests as endocarditis, vascular infections (aneurysms), and osteomyelitis/septic arthritis, particularly of prosthetic joints.[1] Untreated persistent localized Q fever has high fatality. A separate phenomenon, known as post-Q fever fatigue syndrome, is possible in any infected individual. This syndrome is also nonspecific and can present with fatigue, nausea, insomnia, short-term memory loss, headaches, myalgias, and arthralgias.[1]

Criteria for the diagnosis of Q fever include appropriate history, physical exam, and laboratory evidence (polymerase chain reaction [PCR] or serology) of infection (Table). Additional laboratory abnormalities to support acute Q fever are nonspecific and frequently include mild transaminase elevations, thrombocytopenia, and either leukopenia or leukocytosis. The antibody response to Coxiella burnetii infection occurs in 2 antigenic phases: phase I and phase II. Therefore, the patient's serum is collected and tested against phase I and phase II IgG antibodies. A fourfold rise in a patient's phase II titer between an acute and convalescent sample is confirmatory for acute Q fever, and a phase II titer of 1:128 or greater is strongly indicative of acute Q fever. In acute Q fever, the phase II antibody titer is higher than the phase I. A phase I titer of 1:1028 or greater, along with an identifiable source of infection (eg, endocarditis, osteoarticular arthritis, osteomyelitis, vascular infection, chronic hepatitis, pneumonitis), is diagnostic of persistent localized Q fever (Table). Phase I and II titers may be falsely negative in the first 1 to 2 weeks of symptom onset, thereby highlighting the importance of acute and convalescent titers. During these first 2 weeks, if there is high suspicion or known exposure, diagnosis via PCR is possible.[1] If PCR is not available and a high clinical suspicion exists, antibiotic treatment should be initiated while awaiting serologic results.

As mentioned above, many cases of acute Q fever are self-limited and resolve without antibiotic treatment. However, symptomatic patients should be treated with antibiotics to decrease the duration of illness, severity of symptoms, and risk of progression to persistent localized Q fever. The recommended treatment for symptomatic acute Q fever is oral doxycycline for 14 days. Children with acute Q fever should also be treated with doxycycline, which has a low incidence of severe side effects if administered for less than 21 days. Asymptomatic pregnant patients, identified by screening for high-risk exposures or occupations, also should be treated due to the risk of severe maternal complications and poor fetal outcomes. Pregnant patients are treated with trimethoprim-sulfamethoxazole (TMP-SMX) throughout pregnancy. Additional folic acid supplementation is administered to reduce the theoretical risk of congenital abnormalities. TMP-SMX, minocycline, clarithromycin, and ciprofloxacin are alternatives if allergies or other contraindications to doxycycline exist. Patients with a history of cardiac valvular stenosis, prosthetic valve, cardiomyopathy, or aortic aneurysms are at higher risk for developing persistent localized disease and need longer

treatment courses with 12 months of doxycycline and hydroxychloroquine. Patients with invasive or persistent localized disease need longer treatment regimens and adjunctive hydroxychloroquine for 18 to 24 months. There is limited data about the most effective treatment for persistent localized Q fever in children.

Follow-up titers are typically recommended after completion of therapy for acute Q fever. The timing for obtaining titers depends on the patient's risk of progressing to persistent localized Q fever. Titers are generally repeated 6 months after diagnosis in healthy, low-risk individuals and every 3 to 6 months for 2 years after diagnosis in high-risk patients (eg, pregnant patients or those with cardiovascular risk factors).[1] In this case, our patient had titers repeated 3 months and 12 months after completion of therapy, which were stable and decreasing, respectively. Persistently elevated or increasing IgG titers, along with clinical suspicion, warrant further evaluation for persistent localized infection. Our patient's decreasing titers at 12 months and normal echocardiogram were both reassuring against persistent localized infection.

Patients undergoing prolonged therapy (ie, greater than 2 weeks) should have titers followed during and after treatment.[1] Consultation with an infectious disease specialist can be helpful during the diagnosis and treatment of a patient with suspected Q fever to assist in the timing and interpretation of Q fever antibody titers. In addition, their involvement is essential in the management of pregnant patients with Q fever and persistent localized Q fever in children. In our case, the primary care and pediatric infectious disease teams worked closely in the treatment and management of our patient.

Once *Coxiella burnetii* is in the environment, it is very difficult to eliminate. While a vaccine for Q fever is available in Australia for agricultural workers, it is not used routinely in the United States.[1] Instead, other prevention measures are recommended, such as educating farmers about Q fever, avoiding consumption of unpasteurized milk on farms with any known cases, routine animal testing for Q fever, and standard biosafety measures. It is recommended that disposable gloves, protective clothing (washable or disposable coveralls and rubber boots), eye protection, and properly fitted N95 or higher respirator mask be used when calving cattle.[1,2]

CONCLUSIONS

Q fever is a rare zoonotic disease with variable and nonspecific symptomatology that makes it difficult to diagnose. Farmers and others who work with animals are at higher risk, and clinicians should consider acute Q fever in such patients who present with a persisting, nonspecific febrile illness. Serologic testing is used to confirm Q fever cases, and antibiotic therapy can reduce symptom duration and decrease the risk of complications. Persistent localized Q fever and post-Q fever fatigue syndrome are potential complications that should be considered in any person with a history of prior Q fever infection or occupational exposure.

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